

IN THE SPECIFICATION:

Between Abstract and Column 1. Please incorporate the enclosed paper copy of the substitute SEQUENCE LISTING into the application on the page following the Abstract.

Column 1, para. 2. (Amended) LHRH is a small 10 amino acid long peptide (decapeptide) from the hypothalamus. The amino acid sequence (with, as usual, the amino terminal amino acid to the left and the carboxy terminal amino acid to the right) of LHRH is according to the formula in which the amino acids are coded with the three-letter code: pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂ (SEQ ID NO:1), or in the one letter code according to the formula: #E H W S Y G L R P G@ (SEQ ID NO:1), #E is pyroglutamic acid and G@ is glycine amide.

Column 3, para. 2. (Amended) Recently, however, we have shown that it definitively is possible to elicit an effective antibody response in all individuals vaccinated against LHRH (Meloan et al., Vaccine 12, 741-746 (1994)). In these experiments pigs were vaccinated twice with an LHRH vaccine that departs from the "classical" type of LHRH vaccine (LHRH coupled to a carrier protein, in Freund's adjuvant), namely the tandem-LHRH vaccine (European patent nr. 0464124). According to the invention of the tandem-LHRH vaccine there is preferred a peptide which is characterised in that it comprises at least 2 LHRH sequences in tandem according to the general formula (with the amino terminal amino acid to the left and the carboxy terminal amino acid to the right) Z¹-Glx-His-Trp¹-Ser-Tyr-Gly-Leu-Arg-Pro[-Gly-X-Gln-His-Trp²-Ser-Tyr-Gly-Leu-Arg-Pro]_n-Gly-Z² (SEQ ID NO:2), in which amino acids are designated according to the three-letter code, Trp¹ and Trp² are tryptophan (Trp) or formylated tryptophan (N_(indole)-formyl-tryptophan), n is a number having a value of at least 1, X is either a direct bond or a spacer group between the amino acids Gly and Gln, Z¹-Glx is either pGlu (pyroglutamic acid) or Gln having attached thereto a tail comprising one or more additional amino acids, and Gly-Z² is either Gly-NH₂ or Gly having attached thereto a tail comprising one or more additional amino acids. In this general formula, X may be a direct bond between the amino acids glycine and glutamine, i.e., these amino acids are interconnected directly without an intermediate link (via the normal peptide bond). The tandem-LHRH vaccine invention also comprises peptides in which the LHRH sequences are interconnected via spacers. The nature of the spacer group may

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concl

greatly vary from one or more amino acids to a shorter or longer hydrocarbon chain and other compound groups or molecules. In the above general formula, Z¹-Glx preferably stands for pGlu (pyroglutamic acid), but can also stand for Gln having attached thereto a tail comprising one or more additional amino acids, e.g., to be used for coupling of the peptide to a carrier protein. In the above general formula, Gly-Z² stands for, e.g., Gly-NH₂, or Gly having attached thereto a tail comprising one or more additional amino acids, e.g., to be used for coupling of the peptide to a carrier protein. Preferably, Gly-Z² stands for Gly-Cys-NH₂, the C terminal cysteine being added in connection with a possible coupling of the peptide to a carrier protein.

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Column 3, para. 3. (Amended) More in particular, the tandem-LHRH vaccine invention provides a peptide which is characterised in that it comprises at least 2 LHRH sequences in tandem according to the general formula (with the amino terminal amino acid to the left and the carboxy terminal amino acid to the right) pGlu-His-Trp¹-Ser-Tyr-Gly-Leu-Arg-Pro[-Gly-Gln-His-Trp²-Ser-Tyr-Gly-Leu-Arg-Pro]_n-Gly-Cys-NH₂ (SEQ ID NO:3), in which amino acids are indicated according to the three-letter code, Trp¹ and Trp² are either Trp or N-formyl-Trp, and n is a number having a value of at least 1.

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Column 5, para. 3. (Amended) The peptide or peptide composition according to the invention contains a consecutive sequence that can be described according to the following general formula (SEQ ID NO:4):

1 6 16 21
#EHWSY*LRPGQHWSY*LRPGC

in which * indicates possible replacement of Gly by a dextrorotatory amino acid which in addition contains a side chain by which the LHRH tandem unit can be coupled to a carrier compound.

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Column 6, para. 1. (Amended) More in particular, a concrete example of such a preferred peptide according to the invention, a D-Lys⁶-tandem-LHRH dimer according to the following formula:

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cond.

1	6	16	21	
#EHWSY*LRPGQHWSY*LRPGC				(SEQ ID NO:4) * = D-Lys
#EHWSY*LRPGQHWSY*LRPGC				(SEQ ID NO:4)
22	27	37	42	

Column 6, para. 2. (Amended) Another concrete example of such a preferred peptide according to the invention is a D-Glu⁶-tandem-LHRH dimer according to the following formula:

A6

1	6	16	21	
#EHWSY*LRPGQHWSYGLRPGC				(SEQ ID NO:4 where * = D-Glu
				residue 16 is Gly)
#EHWSY*LRPGQHWSYGLRPGC				(SEQ ID NO:4 where
22	27	37	42	residue 16 is Gly)

Column 9, para. 1. (Amended) 1) Peptide formula of C-monomer-LHRH-dimer:

A7

1	11	
pEHWSYGLRPGC		(SEQ ID NO:5 where residue 6 is Gly)
pEHWSYGLRPGC		(SEQ ID NO:5 where residue 6 is Gly)
12	22	

Column 9, para. 2. (Amended) 2) Peptide formula of C-tandem-LHRH-dimer:

A8

1	21	
pEHWSYGLRPGQHWSYGLRPGC		(SEQ ID NO:4 where residues 6 and
		16 are Gly)
pEHWSYGLRPGQHWSYGLRPGC		(SEQ ID NO:4 where residues 6 and
22	42	16 are Gly)

Column 9, para. 3. (Amended) 3) Peptide formula of N-tandem-LHRH-dimer (SEQ ID NO:6 where residues 6 and 16 are Gly and residue 21 is glycine amide):

1

21

A9
cond.

CQHWSYGDRPGQHWSYGLRPG@
 |
 CQHWSYGLRPGQHWSYGLRPG@
 22 42

Column 9, para. 4. (Amended) 4) Peptide formula of [D-Nal(2)⁶]-monomer-LHRH-dimer:

A10

1 6 11
 pEHWSY*LRPGC (SEQ ID NO:5) * = [3-(2-napthalenyl)-
 | -D-alanine]
 pEHWSY*LRPGC (SEQ ID NO:5)
 12 17 22

Column 9, para. 5. (Amended) 5) Peptide formula of [D-Nal(2)⁶]-tandem-LHRH-dimer:

A11

1 6 16 21
 pEHWSY*LRPGQHWSY*LRPGC (SEQ ID NO:4) * = [3-(2-napthalenyl)-
 | -D-alanine]
 pEHWSY*LRPGQHWSY*LRPGC (SEQ ID NO:4)
 22 27 37 42

Column 9, para. 6. (Amended) 6) Peptide formula of [D-Lys⁶]-monomer-LHRH-dimer:

A12

1 6 11
 pEHWSY*LRPGC (SEQ ID NO:5) * = [D-lysine]
 |
 pEHWSY*LRPGC (SEQ ID NO:5)
 12 17 22

Column 10, para. 1. (Amended) 7) Peptide formula of [D-Lys⁶]-tandem-LHRH-dimer:

A13

1 6 16 21
 pEHWSY*LRPGQHWSY*LRPGC (SEQ ID NO:4) * = [D-lysine]
 |
 pEHWSY*LRPGQHWSY*LRPGC (SEQ ID NO:4)
 22 27 37 42

Column 10, para. 4. (Amended)

1) Peptide formula of Tandem-LHRH (SEQ ID NO:4
where residues 6 and 16 are Gly):

1 21
pEHWSYGLRPGQHWSYGLRPGC

Column 10, para. 5. (Amended)

2) Peptide formula of Tandem-LHRH-dimer:

1 21 (SEQ ID NO:4 where residues 6 and
pEHWSYGLRPGQHWSYGLRPGC 16 are Gly)
|
pEHWSYGLRPGQHWSYGLRPGC (SEQ ID NO:4 where residues 6 and
22 42 16 are Gly)

Column 15, para. 3. (Amended)

Peptide formula of [D-Lys⁶]-tandem-LHRH- dimer:

1 6 16 21 (SEQ ID NO:4) * = [D-lysine]
pEHWSY*LRPGQHWSY*LRPGC
|
pEHWSY*LRPGQHWSY*LRPGC (SEQ ID NO:4)
22 27 37 42